Chapter

Congenital Heart Disease and Surgical Outcome in Down Syndrome

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Abstract

The prevalence of congenital heart disease has accounted for nearly one-third of all significant congenital anomalies worldwide. The first report about an association between cardiac anomalies and Down Syndrome was in (1876). Ten years after discovering of Down Syndrome and the credit of association between congenital cardiac anomalies and mongolism was suggested in (1894) by Garrod. There many studies performed to identify a correlation between genotype and phenotype in Down Syndrome, little is known about cardiovascular phenotype in Down Syndrome. Congenital heart disease is considered one of the highest causes of mortality and morbidity in Down Syndrome compared to patients with the same lesion of non-down. There is a big debate about surgical management and considered them as risk factors of surgery with precaution and recent technology, Down Syndrome considered as a normal patient in prognosis. This chapter aimed to shed the light on congenital heart disease in Down Syndrome and current knowledge in specific mutations associated with them and how the effect of innovative technology and management to treat them end at the same outcome and sometimes better based on recent research and Scoring System.

Keywords: Down Syndrome (DS), congenital heart disease (CHD), genetic mutations, surgical outcome, cardiovascular surgery

1. Introduction

1.1 History of congenital heart disease in Down Syndrome

Down Syndrome had a widespread revolutionary widespread interest since the days of Langdon Down's pioneering work in 1866 [1]. The first comprehensive description of this unique syndrome was provided in a short paper published in the London Hospital Reports [2]. Down's article was still unappreciated ten years later. In the July 1876 issue of the *Journal of Mental Science*, other reports on the same subject described the distinguishing features of an apparently new class of "idiots", and the first graphical illustration in the medical literature of DS was drawn in an article by Fraser and Mitchell. This also provided the first pictorial sketch of the facial features of a person with DS [3].

Awareness of DS medical reports was sketchy. It is almost incredible that DS was unknown before the last half of the nineteenth century [4]. In the 1960s,

Figure 1.
The child looking over his mother's shoulder could be erroneously diagnosed as being affected with Down syndrome. Sir Joshua Reynolds's painting (1733) entitled Lady Cockburn and Her Children, which hangs in the National Gallery in London.

Iowa pediatrician Hans Zellweger was excited to find an illustration of a Down patient prior to the latter half of the nineteenth century. **Figure 1** A Down infant appeared in a painting by the Flemish artist Jacob Jordan entitled "Adoration of the Shepherds". This painting is dated 1618 and shows a woman holding a child (probably their daughter, Elizabeth) with similar DS features [5].

Other researchers have searched the art archives to determine pictorial representations of Down patients. In 1968, Dr. Arthur Markingson wrote a letter to the editor of Lancet in which he reported no painting of a Down patient could be found [6]. Dr. Markingson's letter prompted cogent reasons for the apparent rarity of Down children in past centuries. Populations were much smaller than they are now, and the population age structure was different only about two-thirds of females survived to the age at which they could marry. Only half reached the end of childbearing age. Infant mortality was also much higher.

In his opinion, this limited survival of infants with DS in history. In While there were fewer people, the rate of Down births would not have changed appreciably. This suggested that many Down children in the prior centuries did not survive the neonatal period. Thus, raises the question of why did they die? Many reasons must be considered. First, there were no modern therapies such as antibiotics and heart surgery. Down infants often die due to pulmonary infection and heart defects during the critical early years of life. CHD especially likely increased mortality [4–6].

2. Causative gene mutation

Congenital heart is a major public issue and health challenges. Understanding the molecular genetic mechanism underlying abnormal cardiac lesions associated

with trisomy chromosome 21 may lead to novel therapies [7–10]. DS is the most common genetic causes of CHD and characterized by the presence of an extra full or partial human chromosome 21. In recent decades, significant efforts have been made to find the genotype-phenotype correlations for CHD in DS (DS CHD). For earlier detection and prevention and discover a better treatment.

There were several approaches to this problem: generating of a map of partial trisomy (PT21) cases in humans, creating mouse models with different orthologous regions of Hsa21, and analysis of DS gene expression in cells and tissues [11, 12]. Recent studies support the idea that not all Hsa21 loci are required for DS manifestation, suggesting a small region on 21q22.13 is considered critical to the DS core phenotype [13].

A primary goal of genetic studies in DS is to define sub-genomic areas associated with various DS phenotypes. There have been some exciting developments in this area after systematic analysis of 125 subjects from 1973 to 2015 (Pellerin et al., 2016). Retrospective reanalysis of the same cases added seven new topics (Piovesan et al., 2019) [13]. This work built a final map genomic region and discovered 34-kb on the distal part of 21q22.13 highly restricted DS critical region (HR-DSCR). Unfortunately, some patients carried additional chromosomal anomalies which makes the interpretation of genotype-phenotype correlation, including heart defects more difficult. Because of these complications, mice have been used instead of human partial (segmental) Ts21.

The long arm of Hsa21 has 33.9 Mega base in length and contains 430 protein-coding genes; 293 have a homolog in the mouse genome, and only 235 genes are conserved in syntonically regions on mouse chromosomes: (1) 16 (Mmu16, 23.3 Mb, 166 genes), (2) 17 (Mmu17, 1.1 Mb, 22 genes), and (3) 10 (Mmu10, 2.3 Mb, 47 genes). We found that Mmu16 is the only mouse chromosome associated with heart defects in DS [14, 15].

Mouse models associated with congenital heart disease are shown in **Figure 2**. The first is the Tc1 mouse model, which carries Hsa21, where approximately 8% of its genes were deleted leading to heart defects [16, 17]. The second is Ts65D, which is the most widely used model [18]. And exhibits some major DS phenotypes, including heart defects [19, 20]; Ts65Dn is trismic for 13.4 Mb of the 22.9 Mb Hsa21 syntenic region on Mmu16. The cardiovascular phenotype of overlapping in larger-than-5.8 Mb sub-centromeric region on Mmu17, which is not syntactic to any region on Hsa21 [21].

We recently developed new rodent models to understand and mimic DS mouse segmental trisomy. The third type of model is Dp (10)1Yey/+, Dp (16)1Yey/+ and

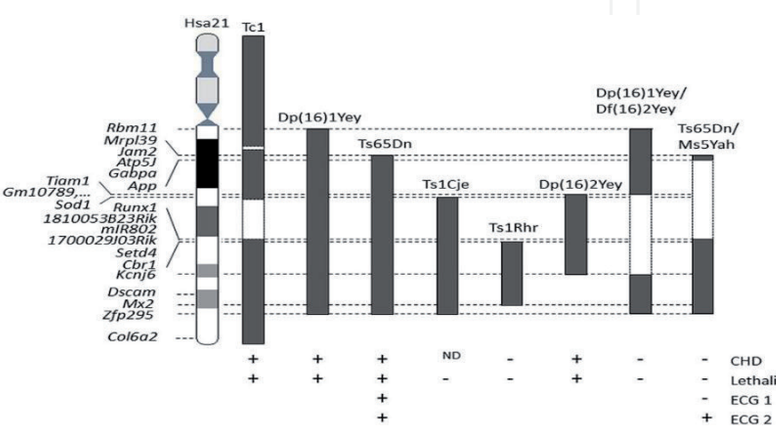

Figure 2.
Representation of the DS mouse models associated with cardiac features. "+" indicates the presence and "-" the absence of phenotypes whereas ND indicates a non-determined state for presence or absence of CHD in Ts1Cje.

Dp (17)1Yey/+, carrying individual duplications spanning the entire Hsa21 syntenic regions on Mmu10, Mmu16, and Mmu17, respectively. The results showed both Dp (16)1Yey/+Dp (10)1Yey/+; Dp (16)1Yey/+; and Dp (17)1Yey/+ contribute to heart defects with similar frequency. The final model showed heart defect in Dp (16)2Yey/+ embryos within the Tiam1-Kcnj6 region correlated with over-expression of 20 genes in this area [22].

CHD in DS is a phenotype characterized by reducing the extent to which a particular gene or set of genes expressed in the phenotypes of individuals carrying it. Consequently, in PT21 cases mapping, it is possible to exclude chromosomal regions or identify them as critical for the phenotype only in patients with that phenotype (DS CHD). Approaching the DS CHD critical region was proposed by Korenberg et al. [23] when his concept used the 9 Mb region between D21S55 (21q22.2) to the telomere for the first time. This work further used mouse models over 4–5 Mb region, from (D21S55 through MX1) Korbel et al. [24] narrowed down the critical part for DS CHD to 1.77 Mb, **Figure 3**. The region in question was extended from DSCAM to ZNF295 (current name ZBTB21) created from combining the maps of 14 PT21 subjects with CHD with information from segmental trisomic mouse model Dp (16)1Yu/+.

In 40–60% of subjects, the overall risk of DSCHD in DS is from AVSDs [25]. Although some candidate genes have been a cause for DSCHD, conclusive evidence for their involvement is still unknown. We previously reported a map that contains the DSCHD region in humans to a 5.27-Mb chromosomal segment containing 82 genes [26]. **Figure 3A** narrows down this segment to a 2.82-Mb critical region likely involved in DSCHD endocardial cushion defects using an expanded panel with 14 subjects with DSCHD. By integrating our information from segmental trisomic mouse models with DSCHD [16, 21], we integrated a further limit on this region in a particular map (**Figure 3B**); we propose a 1.77-Mb DSCHD critical region, which contains ten genes, including the promoter and a portion of the DS cell adhesion molecule (DSCAM) gene. Specifically, the model Dp (16)1Yu/shows that DSCHD is involved only in the HSA21 regions orthologous to MMU16 (located at 14.4 Mb–42.3 Mb of HSA21); this defines the telomeric DSCHD border and suggests a limited role for the adjacent telomeric region for DSCHD.

2.1 Genes associated with causing CHD

A multifactorial model used as sample collection. Chromosome 21 Single nucleotide polymorphisms calling and Chromosome 21 Copy number variations analyses by pyrosequencing and Sanger sequencing showed most notable results of this study regarding identifying CHD risk loci in DS [27].

1. rs2832616 and rs1943950 are CHD risk alleles (odds ratios of 2.8 and 2.7, respectively) within the same LD block on chromosome 21 (both cis-eQTLs for KRTAP7–1 gene).

2. A 4.9-kb CNV upstream of the RIPK4 gene (CNV1) the RIPK4 gene (CNV1) has a risk ratio of 2.29 in the previously reported CHD region of chromosome 21.

3. A 1.8-kb CNV within the ZBTB21 gene (CNV2) of chromosome 21 with a risk ratio of 1.85. in the previously reported CHD region.

4. A pair of interacting cis-eQTLs on chromosome 11 (Bonferroni-adjusted P-value <0.05). involving CNOT11 on chromosome 2 and NRGN.

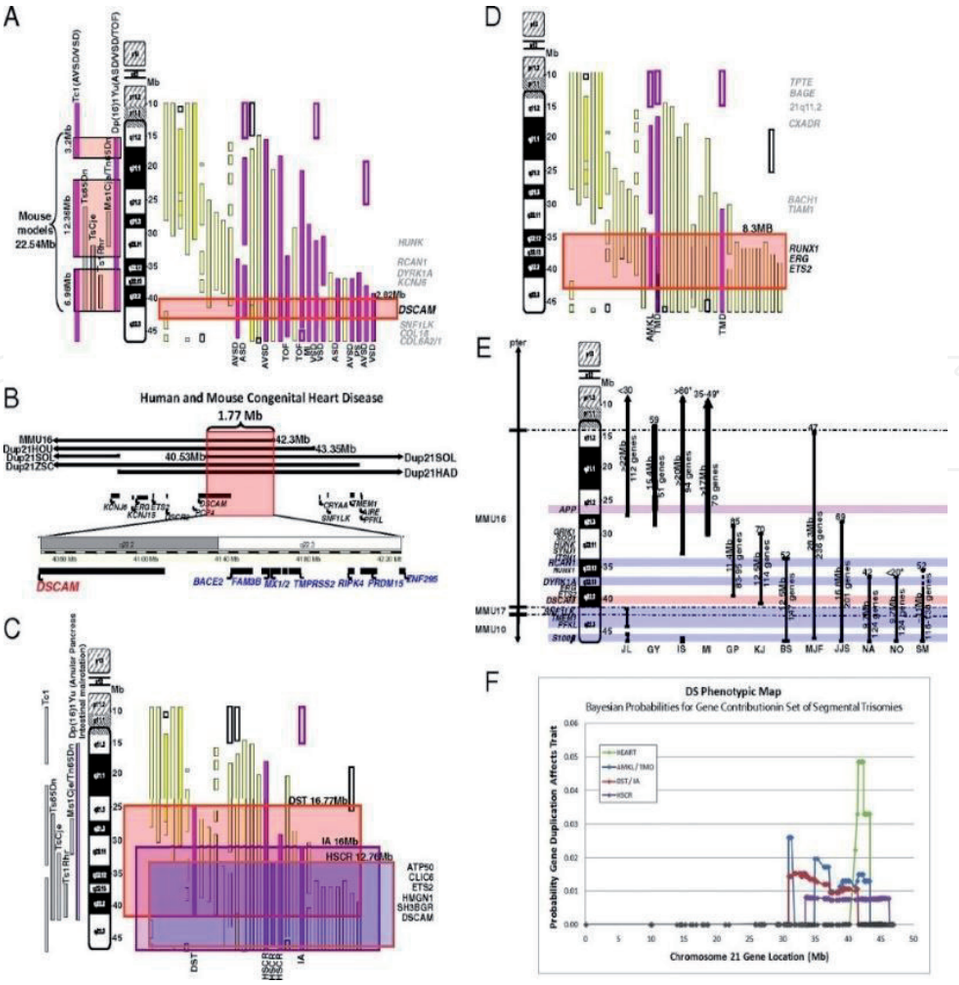

Figure 3.
A panel of 30 patients with segmental trisomy 21 metanalysis defines DS phenotype candidate regions. Yellow boxes, no phenotype; solid boxes, increased copy-number; open boxes, 1:2 (monosomies) Purple boxes, presence of phenotype. (A) DSCHD region. TOF, tetralogy of Fallot; PS, pulmonic stenosis; PDA, patent ductus arteriosus; VSD, ventricular septal defect; ASD, atrial septal defect; MI, mitral insufficiency. Red box, DSCHD candidate region. Twenty-three subjects have duplications, including the DSCHD region, 14 thereof have DSCHD. No subject lacking a segmental trisomy involving the DSCHD critical regions was diagnosed with DSCHD. Corresponding regions for six mouse models are indicated to the left [21, 22, 39–41]. (B) Proposed DSCHD critical region (red box) determined by combining human and mouse data from A. MMU16 indicates the extent of the duplication in the mouse model Dp (16)1Yu with DSCHD.

3. Clinical management

3.1 Diagnostic evaluation

Echocardiograms are generally accepted as the diagnostic standard. Some studies specified that all had an echocardiogram [49], while others limited by documentation and relied on retrospective review [28]. One study evaluated if screening, chest X-ray and ECG is an effective method to identify which infants with DS should have an echocardiogram. They found that this method resulted in 69 (17%) fewer echocardiograms without missing infants with major CHD [29]. A similar study showed a sensitivity of 71% and a specificity of 91% chest X-ray and ECG soon after birth for three modalities separately or in combination to detect CHD [30].

3.2 Surgical approach

DS is a challenging public health issue. The survival rate of DS with heart defects has increased dramatically with improved medical care [31]. Infant mortality for

patients with DS remain 5× to 8× higher than that of the general population. In the 1940s to 1960s, the average life expectancy for children born with DS dramatically increased from 12 years in the 1940s to 60 [32]. There has been a gradual improvement in the results of DS children undergoing cardiac surgery in the last 16 years [33] with a better understanding of surgical anatomy, Advances in surgical techniques improved myocardial protection and cardiopulmonary bypass strategies, and advances in postoperative management in the intensive care unit contributed to improved survival rate and decreased mortality [34–36].

When comparing the DS to NS in preoperative data, however there are significant differences in age, RACHS-1 risk category, and presence of substantial noncardiac anomalies among DS patients in the 30 days (about four and a half weeks) to 1 year age group. In contrast, most children in the non-DS patients were in the >1 year age group. The DS population is more likely to have a coexisting major noncardiac structural anomaly, although DS were less likely to have been born prematurely [32].

In open-heart surgery, the cardiopulmonary bypass led to prolonged times. [(110 ± 47 min), 129 (87.75%), and (101.74 ± 33.61)]; aortic cross-clamp was shorter [(65 ± 30 min), 64 minutes (67.21 ± 26.63)]. Depend on the scoring system most patients in DS and Non-DS, RACHS-1 risk categories 1, 2, and 3. Distribution for patients without DS were spread across these three risk categories. In DS, the proportion of patients in risk categories 1, 2, and 3 increased with increasing surgical complexity [32, 37].

Infection is the most common complication that feared by surgeons and results in a more prolonged ICU and hospitalization with considerable treatment in patients with CHD and DS [38]; respiratory complications are also common. Sepsis occurred in 8 patients (10%), mainly caused by Staphylococcus and Pseudomonas. In 7/8 cases, this infection occurred early in the postoperative period. In one case, sepsis developed late and led to death [33].

4. Types of producers associated with DS

4.1 Favorable surgical outcome

4.1.1 Complete atrioventricular septal defect

Hospital mortality ranges from 0.9 to 3% in recent studies [39, 40]. The degree of residual valve dysfunction was independent of surgical choice in a study comparing three surgical techniques [41]. LV outflow tract obstruction is the second cause for reintervention small left ventricle (LV) and a double orifice left the atrioventricular valve. There was an anatomic increase in reoperation incidences, such as a small left ventricle (LV) and a double orifice left atrioventricular valve [41]. The hospital resources usage for cardiac surgery in pediatric patients with CHD and genetic conditions is of great interest [42]. Patients with DS and AVSD heart defect did not constitute an extra financial burden due to good surgical outcome and short hospital stay.

4.1.2 Partial atrioventricular septal defects

Mortality rate was low (0–1%) and reported with repair performed in early childhood [43]. The left atrioventricular valve anatomy was unfavorable in 31% of cases. Reoperation was required in 22% of non-DS. All patients survived surgery.

Other issues include:

4.1.3 single ventricle physiology and Unbalanced atrioventricular septal defects

There is often univentricular palliation or correction (Fontan-type) due to the constant risk of pulmonary hypertension or even mildly elevated pulmonary vascular resistance. Excellent survival was noted at palliation when pulmonary vascular resistance was low (<3 Wood Units/m2) in the 1st year of life. The mortality rate of patients with Fontan-type repair was 27.5% in patients with unbalanced AVSD [44]. Moreover, Fontan-type repair was rarely performed and was considered risky (12% early mortality) in Japan [45]. Furukawa et al. reported eight patients with Down syndrome who underwent total cardiopulmonary connection; one patient died, whereas the clinical course and recovery after surgery in the other seven patients was significantly prolonged. They studied 17 patients with DS who underwent TCPC and reported that mortality in the early period was 29% and significantly higher than that in patients without DS (10%). The debate is now DS itself is a vital independent factor of mortality. Future work should evaluate mortality and long-term prognosis.

4.2 Unfavorable surgical outcome

4.2.1 Tetralogy of Fallot

Cyanosis in DS patients accounts for about 6% of deaths. Early mortality has been reduced to 1–2% in recent years [39, 46, 47]; pulmonary hypertension is presumed to be a causal factor, and this was supported by its higher incidence in patients with tetralogy of Fallot associated with AVSD. Patients with DS and tetralogy of Fallot need a pulmonary valve replacement (PVR)/implantation earlier than normal patients [48].

4.2.2 Tetralogy of Fallot combined with AVCanal

This is a rare anomaly frequently associated with DS and low operative risk (4–6%) has been recently accomplished Complete repair [49] two-stage (with prior palliation) and single-stage repair was recently reported. With 10-year survival obtained the two strategies as well as similar freedom from reoperation for left atrioventricular valve regurgitation [50].

5. Scoring systems in cardiac surgical outcome

5.1 RACHS-score

The RACHS-1 method [51, 52] was used to adjust for differences in the patient mix when comparing in-hospital death. Surgical procedures ranged from 1 to 6 risk categories. Risk category 1 has the lowest risk for in-hospital death, whereas risk category 6 has the highest. Risk categories 5 and 6 were combined for reporting purposes because of the low numbers of patients in each group. Patients with >1 cardiac surgical procedure were placed in the category of the highest risk procedure.

Two studies evaluated outcomes in children with DS by grouping cardiac lesions based on risk-stratified categories (RACHS-1). There were generally low mortality rates for children with DS compared to those without, which highlighting the higher rate of cardiac operations in DS children [32, 39].

5.2 Aristotle score

A new international Nomenclature of evaluating the quality of care in congenital heart surgery based on the complexity of the surgical procedures the project started in 1999, involving expert surgeons included 50 pediatric surgeons from 23 countries representing International Scientific Societies. The calculation is undertaken in two steps: the first adjusts only the complexity of the procedures by establishing the Basic Score determined by three factors: the potential for morbidity, the anticipated technical difficulty, the potential for mortality. The second step was improving the Comprehensive Score, which further adjusts the complexity according to the specific patient characteristics. The Aristotle method allows the following equation of quality of care: Complexity FN Outcome = Performance which allows precise scoring of the complexity for 145 congenital heart surgery procedures. The complexity was based on the procedures defined by the Society of Thoracic Surgeons (STS)/European Association for Cardiothoracic Surgery (EACTS) [53].

5.3 Propensity score matching analysis

Propensity score matching was frequently used in the cardiovascular surgery literatures. These methods are increasingly used to reduce the impact of treatment-selection bias in estimating causal treatment effects using observational data [54–56]. Tóth et al. reported that the perioperative values had no significant differences between the DS and non-DS groups after propensity matching. This method used similar values for the variables and can play an essential role in identifying the differences between control and study groups.

In *Seminars in Thoracic and Cardiovascular Surgery,* the propensity score used at 5:1, (NS: DS). PSM based on sex, low birth weight, and prematurity age group with post matching standardized mean difference indicating successful balancing of the two groups; the final matched set was 2493 DS patients. These were compared to 12,465 patients, as shown in **Figure 4**.

We show outcomes after cardiac operations in patients with DS using Texas Inpatient Public Use Datafile was queried for all patients <18 years old undergoing

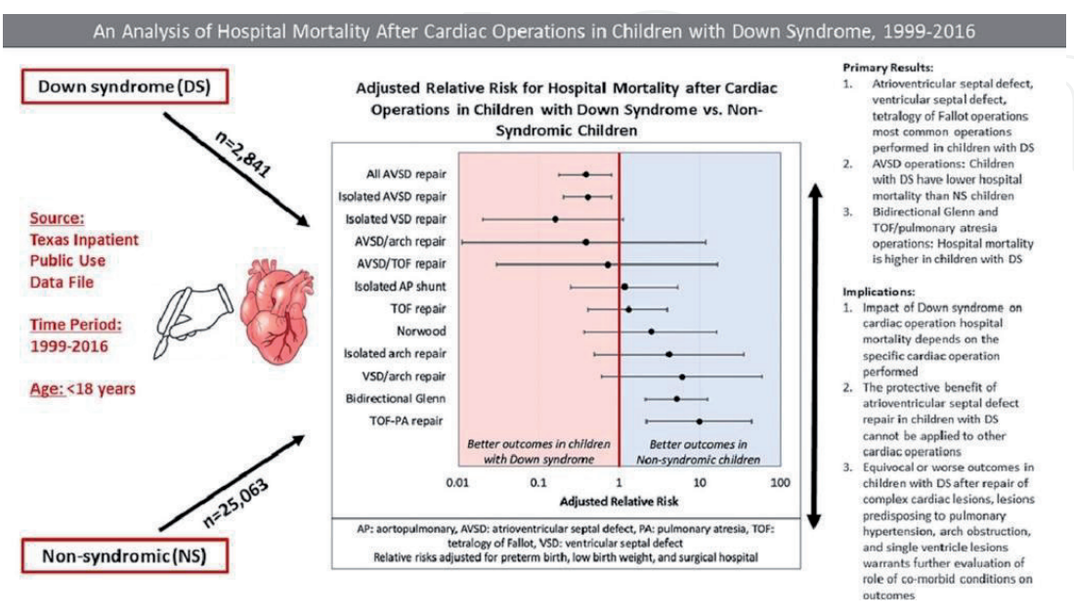

Figure 4.
Children with Down syndrome and non-syndromic children undergoing various cardiac operations represented by The Texas Inpatient Public Use Datafile was queried from 1999 to 2016.

CHD procedures between 1999 and 2016. There were 2,841 cases in DS patients who underwent CHD operations compared to 25,063 non-DS cases. Over the 18-year period. Variables depending on the type of CHD lesion when multiple cardiac lesions require intervention; DS children have an excellent surgical outcome and hospital survival after isolated AVSD than did non-DS children. Bidirectional Glenn palliation TOF/PA repair was associated with worse hospital mortality in children with DS. Further work will be evaluated cardiac and noncardiac comorbidities in DS patients led to higher mortality for specific cardiac lesions [57].

6. Conclusion

The challenge of cardiac care of DS patients has no more concerns because of a great improving result of cardiac surgery contribute to the increasing survival and to the better quality of life is even more successful and gratifying.

Conflict of interest

The authors declare no conflict of interest.

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